#14 B
PT 8/22/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Andrew W. Shyjan *et al.*

Serial No.: 09/374,554

Filed: August 13, 1999

For: *Methods and Compositions for the Identification and Assessment of Cancer Therapies*

Attorney Docket No.: MRI-005CP2CPA

Group Art Unit: 1634

Examiner: Goldberg, J.

Commissioner for Patents
Washington, D.C. 20231

Certificate of First Class Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on the date set forth below.

August 13, 2002
Date of Signature and of Mail Deposit

By: _____
DeAnn F. Smith
Reg. No. 36,683
Attorney for Applicants

AMENDMENT AND RESPONSE

Dear Sir:

This is in response to the Office Action (Paper No. 11) dated February 13, 2002 in the above-referenced application. A request for a three-month extension of time and the appropriate extension fee based on large entity status are filed concurrently herewith. Please amend the specification and claims as follows:

In the Specification:

Please replace the priority information at the top of page 1 of the specification with the following paragraph,

B1

This application is a Continued-Prosecution-Application and claims priority under 35 U.S.C. §120 to Continued-In-Part U.S. application Serial No. 09/374,554, filed August 13, 1999, and Continued-In-Part U.S. application Serial No. 09/322,864, filed on May 28, 1999. The contents of each of the aforementioned applications are expressly incorporated by reference.

Please replace page 1, line 35 through page 2, line 9 of the specification with the following paragraph,

B2

In the realm of cancer therapy it often happens that a therapeutic agent that is initially effective for a given patient becomes, overtime, ineffective or less effective for that patient. The very same therapeutic agent may continue to be effective over a long period of time for a different patient. Further, a therapeutic agent that is effective, at least initially, for some patients can be completely ineffective or even harmful for other patients. Accordingly, it would be useful to identify genes and/or gene products that represent prognostic markers with respect to a given therapeutic agent or class of therapeutic agents. It then may be possible to determine which patients will benefit from particular therapeutic regimen and, importantly, determine when, if ever, the therapeutic regime begins to lose its effectiveness for a given patient. The ability to make such predictions would make it possible to discontinue a therapeutic regime that has lost its effectiveness well before its loss of effectiveness becomes apparent by conventional measures.

Please replace page 35, lines 9-18 of the specification with the following paragraph,

B3

Activity database (A)

Two tables were created: a table consisting of the growth inhibition (GI_{50}) values for 54 of the 60 cell lines and 171 compounds was created from the NCI-DTP *in vitro* cancer screen database. These were the seed compounds representing the major classes of compounds present in the larger 23,000 compounds database available from the DTP. The seed compounds were selected on the basis of their known mechanism of action and chemical structure. The average potency $-\log\{GI_{50}\}$ was extracted from the flat comma-delimited text files. Missing values were left as a blanks in the data tables.

Please replace page 36, lines 1-8 of the specification with the following paragraph,

B4

The isolated polyA RNA (2 μg) was used to synthesize cDNA using Gibco BRL Superscript Choice System cDNA Synthesis Kit. The following modified T7 RNA polymerase promoter -[T]24 primer was used:

5'-GGCCAGTGAATTGTAATACGACTCACTATAGGGAGGCGG-[T]24-3' (SEQ ID NO:1)

Please replace page 45, lines 6-27 of the specification with the following two paragraphs,

B5

In the second study, nucleic acid arrays were used to determine the level of expression of approximately 6500 nucleic acid sequences in a relatively TAXOL resistant human mammary epithelial cell primary cell line (HMEC) and in a relatively TAXOL sensitive breast cancer cell line (MDA-435) in the presence of TAXOL. This analysis led to the identification of genes that are relatively highly expressed in the TAXOL resistant human mammary epithelial cell primary cell line compared to the relatively TAXOL sensitive breast cancer cell line (Table 10A) and genes that are relatively highly expressed in the relatively TAXOL sensitive breast cancer cell line compared to the relatively TAXOL resistant human mammary epithelial cell primary cell line (Table 10B).

In the third study, nucleic acid arrays were used to determine the level of expression of nucleic acid sequences in ovarian cancer clinical samples obtained from patients whose ovarian cancer appeared to respond to TAXOL/cisplatin combination therapy over an initial six month treatment period ("TAXOL/cisplatin sensitive clinical samples") and ovarian cancer clinical samples obtained from patients whose ovarian cancer appeared to respond poorly to TAXOL/cisplatin combined therapy over and initial six month treatment period ("TAXOL/cisplatin resistant clinical samples"). This analysis led to the identification of genes that are expressed at a relatively high level in the TAXOL/cisplatin resistant clinical samples compared to the TAXOL/cisplatin sensitive clinical samples (Table 11A) and genes that are expressed at a relatively low level in the TAXOL/cisplatin resistant clinical samples compared to the TAXOL/cisplatin sensitive clinical samples (Table 11B).

Please replace page 46, lines 6-13 of the specification with the following paragraph,

B6 The Affymetrix HUM6000 GeneChip system (Santa Clara, CA) was used to measure expression of approximately 6500 nucleic acid sequences in the selected cell lines. The cRNA used for expression analysis was prepared as follows. First, double passed polyA RNA was prepared from the cell line pellets (~10^8 cells/pellet) using Invitrogen Fast Track 2.0 system. Next, cDNA was prepared from 2μg of polyA RNA using Gibco BRL Superscript Choice System cDNA Synthesis Kit. The following modified T7 RNA polymerase promoter -[T]24 primer was used:

5'- GGCCAGTGAATTGTAATACGACTCACTATAGGGAGGCGG-[T]24-3' (SEQ ID NO:2)

Please replace page 50, lines 22-25 of the specification with the following paragraph,

B7 The clinical samples were obtained from patients undergoing ovarian cancer therapy at the Mayo Clinic (Rochester, MN). Gene expression was measured as described above for the first study of TAXOL resistant and TAXOL sensitive cell lines except that a proprietary nucleic acid array was used to measure expression.

In the Claims:

Applicants cancel, without prejudice, claims 1, 2, 4, 5, 7-11, 13-17, 19-20, 22-26, 28-31, 34, and 37-40.

Please amend claims 3, 6, 12, 18, 21, 27, 32, 33, 35, and 36 as follows:

B8 3. **(Amended)** A method for determining whether TAXOL cannot be used to reduce the growth of breast cancer cells, comprising the steps of:

a) obtaining a sample of breast cancer cells;

b) determining whether said breast cancer cells express the BST-2 gene; and

c) identifying that TAXOL cannot be used to reduce the growth of said breast cancer cells when said BST-2 gene is expressed by said breast cancer cells.

B9 6. **(Amended)** The method of claim 3, wherein said level of expression is determined by detecting the amount of mRNA that is encoded by said BST-2 gene present in said sample.

B10

12. **(Amended)** The method of claim 3, wherein said breast cancer cells are selected from the group consisting of breast cancer cell lines and breast cancer cells obtained from a patient.

B11

18. **(Amended)** A method for determining whether TAXOL cannot be used to reduce the growth of breast cancer cells, comprising the steps of:

a) obtaining a sample of breast cancer cells;

b) exposing the breast cancer cells to TAXOL;

c) determining the level of expression in the breast cancer cells of the BST-2 gene in the sample exposed to the TAXOL and in a sample of breast cancer cells that is not exposed to TAXOL; and

d) identifying that TAXOL cannot be used to reduce the growth of said breast cancer cells when the expression of said BST-2 gene is increased in the presence of TAXOL.

B12

21. **(Amended)** The method of claim 18, wherein said level of expression is determined by detecting the amount of mRNA that is encoded by said BST-2 gene present in said sample.

B13

27. **(Amended)** The method of claim 18, wherein said breast cancer cells are selected from the group consisting of breast cancer cell lines and breast cancer cells obtained from a patient.

B14

32. **(Amended)** A method for determining whether treatment with TAXOL should be continued in a breast cancer patient, comprising the steps of:

a) obtaining two or more samples comprising breast cancer cells from a patient during the course of TAXOL treatment;

b) determining the level of expression in the breast cancer cells of the BST-2 gene in the two or more samples; and

B14 concld

c) discontinuing treatment when the expression level of said BST-2 gene increases during the course of treatment.

B15

33. **(Amended)** A method for determining whether treatment with TAXOL should be continued in a breast cancer patient, comprising the steps of:

a) obtaining two or more samples comprising breast cancer cells from a patient during the course of TAXOL treatment;

b) determining the level of expression in the breast cancer cells of the BST-2 gene in the two or more samples; and

c) continuing treatment when the expression level of said BST-2 gene does not increase during the course of treatment.

B16

35. **(Amended)** The method of claim 32, wherein said level of expression is determined by detecting the amount of mRNA that is encoded by said BST-2 gene present in said sample.

B17

36. **(Amended)** The method of claim 33, wherein said level of expression is determined by detecting the amount of mRNA that is encoded by said BST-2 gene present in said sample.

REMARKS

Claims 1-40 were pending in the instant application. Applicants cancel, without prejudice, claims 1, 2, 4, 5, 7-11, 13-17, 19-20, 22-26, 28-31, 34, and 37-40. Claims 3, 6, 12, 18, 21, 27, 32, 33, 35, and 36 have been amended. Support for amendments to pages 45 and 50 of the specification may be found, for example, at page 3, lines 24-36; at page 50, line 9; and at page 50, lines 10-21 of the specification. Additional support for the amendments to pages 45 and 50 of the specification may be found in the references to ovarian cancer cells lines which are noted in the specification as "OV," for example, at page 48, lines 20-21; at page 48, lines 21-22; at page 50, lines 34-37 of the specification and in Figures 11A and 11B. Support for the

amendments of claims 3, 6, 12, 18, 21, 27, 32, 33, 35, and 36 can be found throughout the specification and the originally filed claims. No new matter has been added. Accordingly, claims 3, 6, 12, 18, 21, 27, 32, 33, and 35-36 are pending.

Attached hereto as Appendix A is a marked-up version of the changes made to the claims and the specification by the amendments presented herein. Appendix A is captioned "Version with markings to show changes made." For the Examiner's convenience, a complete set of "clean claims" that will be pending upon entry of the amendments presented herein is attached hereto as Appendix B.

Amendment and cancellation of the claims herein should in no way be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, or in any previous Office Action, and were done solely to expedite prosecution of the above-identified application. Applicants reserve the option to prosecute the same or similar claims as those originally filed in the instant application or in this or one or more or subsequent applications.

Priority

The Examiner noted on page 2 of the Office Action that "Applicant's have elected BST2 as the single sequence....this appears to receive benefit of the August 13, 1999 date of the instantly filed case." Applicants submit that BST-2 was first disclosed in Table 9B of Application Serial No. 09/322,864 filed on May 28, 1999. Applicants have thus amended the priority information on page 1 of the specification to reflect the correct priority date of the now pending claims.

The Examiner has also noted that the priority section of the specification does not conform to the guidelines set forth in the MPEP §201. Applicants note that the priority information of the parent application was amended in the transmittal of the CPA application filed on March 20, 2001. However, as noted above, Applicants submit herewith amendments to the priority information to reflect the correct priority date of the now pending claims. Accordingly, Applicants request that the Examiner withdraw the objection.

Drawings

The Examiner has objected to the tables for being unclear "with respect to which numbers are designed to be directed to which table headings. Moreover, the text appears to have been copied numerous times blurring some of the letters, words, and numbers." Applicants submit herewith amended tables which correct the informalities noted by the Examiner. With respect to the Examiner's objection to the tables being blurred, Applicants respectfully submit herewith a new set of the tables.

Specification Objection

The Examiner objected to the disclosure "because it contains an embedded hyperlink and/or other form of browser-executable code." In response to the Examiner's objection, Applicants have deleted the embedded hyperlink at page 35, line 17 of the specification.

The Examiner also objects to the blank line at page 45 of the specification. Applicants have deleted the blank line at page 45 of the specification by amendment herein.

Sequence Rules

The Examiner notes that the application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825. In particular, on page 36 and 46, the specification describes a primer, but fails to provide any SEQ ID NO for the sequence. Applicants submit herewith amendments to the specification and a substitute Sequence Listing that provides SEQ ID NOS for the primers described in the specification and complies with 37 C.F.R. 1.821-1.825. Applicants therefore respectfully request that the Examiner withdraw this objection.

Claim Rejections
Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Office Action at page 4 indicates that claims 3, 6, 12, 15, 18, 21, 27, 30, 32, 33, 35, and 36 have been rejected under 35 U.S.C. § 112, first paragraph as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner also cites the *In re Wands* factors to support this rejection.

The Court of Appeals for the Federal Circuit in *In re Wands*, USPQ 2d 1400 (Fed. Cir. 1988) set forth the factors that should be considered when determining whether a disclosure meets the enablement requirement: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims." It is Applicants' position that under these guidelines, the pending claims are fully enabled and satisfy the requirements under 35 U.S.C. §112, first paragraph.

Breadth of the Claims

With reference to the *Wands* factors, the Examiner, at page 4, indicates that "[t]he claims are broadly drawn to methods of determining whether TAXOL cannot be used to reduce the growth of cancer cells, and methods for determining whether or not treatment with TAXOL should be continued in a cancer patient [by] determining the expression level of BST2." Applicants respectfully traverse and submit that one skilled in the art, after reading the specification, could perform the claimed methods without undue experimentation and thus the pending claims are fully enabled.

Sufficient Guidance and Direction Have Been Presented and Multiple Working Examples Are Taught By the Present Invention

In assessing the quantity of experimentation necessary and the amount of direction or guidance presented by the instant specification, the Examiner indicates that:

> [t]he specification teaches cancer cell lines are used to determine whether genes and/or ESTs are sensitive or resistant (page 34)...Example 2, page 40, teaches identification of sensitivity and resistance genes *in vivo*...the specification teaches three studies which are directed to TAXOL. Genes are identified which are relatively highly expressed in TAXOL resistant cell lines. The levels of expression in mammary epithelial cell primary cell lines and breast cancer cell lines were compared. Moreover, breast cancer clinical samples which appeared to respond well and poorly to TAXOL were compared.

Applicants respectfully submit that the present invention provides more than sufficient guidance and direction as to how to perform the claimed methods. Moreover, Applicants teach multiple working examples which illustrate how the methods of the present invention may be performed. Specifically, Applicants teach the identification of BST-2, whose expression is correlated with resistance treatment with TAXOL (see, for example, Example 5). Applicants further disclose methods for determining whether TAXOL will or will not be effective in reducing breast cancer tumor growth (see, for example, page 7, lines 1-25 of the specification) by determining BST-2 expression.

State of the Art

BST-2 Expression

With respect to the state of the prior art, the Office Action indicates that:

> [t]he art teaches that BST -2 is expressed in human cell lines including those with the origin of hepatoma, bladder cell carcinoma, glioblastoma and cervical cancer carcinoma (Ishikawa *et al.* Genomics, Vol. 26, pages 527-534, 1995). Ishikawa also illustrates that BST-2 mRNA are expressed in a variety of tissues including pancreas, kidney, skeletal muscle, liver, lung, placenta, brain and heart.

Applicants respectfully submit that the present invention teaches methods for identifying an agent that cannot be used to reduce the growth of breast cancer cells when the expression of BST-2 is increased in the presence of the agent. In contrast, Ishikawa teaches BST-2 expression generally, not an increased expression under specific circumstances. Thus, the expression of BST-2 in a variety of cell lines is not relevant to the present invention as Applicants have clearly demonstrated a correlation between increased BST-2 expression and TAXOL resistance in breast cancer cells, as claimed.

Taxol Screening Methods

At page 5 of the Office Action, the Examiner asserts that

> [t]he art teaches characterization of taxol-induced apoptosis and altered gene expression in human breast cancer cells (Cheng *et al.* Cellular

> Pharmacology, Vol 2, pages 249-257, 1995). Cheng teaches using a PCR-mediated differential screening procedure and Northern analysis, 12 taxol response genes were identified from human breast tumour cell line that are either up- or down-regulated by taxol (abstract, Table 1).

Applicants submit that the state of the art with respect to screening methods is well established. The instant specification discloses that "isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays" (see page 14, lines 8-10 of the specification). The present invention teaches that a variety of formats may be employed to determine whether a sample contains a protein that binds to a given antibody, such as enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA) (see page 15, lines 30-33 of the specification). Applicants also disclose that "an analysis of the tissue and/or cell type distribution of the mRNA produced by the identified genes can be conducted, utilizing standard techniques well known to those of skill in the art. Such techniques can include, for example, Northern analyses, RT-coupled PCR and RNase protection techniques." (see page 19, lines 9-12 of the specification).

Taxol Sensitivity

The Examiner is further of the opinion that:

> Borbe *et al.*...teaches an analysis of a panel of 12 human glioma cell lines which revealed no relationship between genetic or functional p53 status and taxol sensitivity. Moreover, Borbe teaches 'activity of taxol against malignant glioma cell lines *in vitro* has been shown in several studies. However, despite the remarkable *in vitro* potency of taxol, phase II clinical studies of taxol for primary or recurrent malignant gliomas showed no relevant activity'...As provided in the art, p53 is commonly overexpressed in gliomas...gliomas are part of a subset of tumors in which overexpression of p53 protein in the absence of p53 gene mutation has been described.

Applicants respectfully submit that Borbe *et al.* demonstrates impressive *in vitro* results which were persuasive enough to gain FDA approval for phase II clinical trials. Applicants

further submit that the fact that gliomas overexpress p53 and are resistant to TAXOL is not relevant to the present invention as Applicants have clearly demonstrated a correlation between increased BST-2 expression and TAXOL resistance in breast cancer cells, as claimed.

Cell Lines Are a Useful and Appropriate Model for Studying Tumors

The Examiner cites Demer *et al.*, Orr *et al.*, and Eastham for the proposition that tumor cell lines are not indicative of tumors and demonstrate poor representation of malignancy.

Applicants respectfully submit that tumor cell lines have consistent behavior from passage to passage, thus they are an appropriate and useful model for studying behavior of tumor cells. In contrast, primary culture of tumor cells may be passaged a limited number of times, thus resulting in inconsistent behavior across multiple experiments. Applicants further submit that tumor cell lines are routinely used in the art because the work done in tumor cell lines may be reproduced.

Routine Experimentation and Predictability of the Art

According to the Examiner, the claims are not enabled because of the quantity of experimentation required to perform the claimed methods and the unpredictability of the art. In particular, the Examiner asserts that:

> the specification is confusing as to whether breast cancer patients or ovarian cancer patients were studied on page 50. On page 45, the specification appears to be describing a study which samples breast cancer clinical samples obtained from patients whose breast cancer appeared to respond to TAXOL/cisplatin combination therapy and breast cancer clinical samples which appeared to respond poorly (lines 17-25)...However, on page 50, the specification discusses differential expression of genes in responsive and nonresponsive ovarian cancer...However, the specification also teaches that the clinical samples were patients undergoing breast cancer therapy (lines 22-24). Therefore, it is unclear what data is provided in Table 11A and 11B.

Applicants respectfully traverse the foregoing rejection and respectfully submit that the level of skill in the art in the area of determining RNA and protein expression of a gene, such as BST-2, is quite high, and this technology area is predictable. In Example 5, Applicants

describe three different studies designed to identify genes that are differentially expressed in TAXOL sensitive and TAXOL resistant cancer cells (see page 44, lines 34-35 of the specification). In the first study, nucleic acid arrays were used to determine the level of expression of approximately 6500 nucleic acid sequences in selected relatively highly TAXOL resistant and relatively highly TAXOL sensitive *solid tumor cell lines from the NCI 60 cancer cell line series*. In the second study, nucleic acid arrays were used to determine the level of expression of approximately 6500 nucleic acid sequences in a relatively TAXOL resistant *human mammary epithelial cell primary cell line (HMEC)* and in a relatively TAXOL sensitive *breast cancer cell line (MDA-435)* in the presence of TAXOL. In the third study, nucleic acid arrays were used to determine the level of expression of nucleic acid sequences in *ovarian cancer clinical samples* obtained from patients whose ovarian cancer appeared to respond to TAXOL/cisplatin combination therapy over an initial six month treatment period ("TAXOL/cisplatin sensitive clinical samples") and ovarian cancer clinical samples obtained from patients whose ovarian cancer appeared to respond poorly to TAXOL/cisplatin combined therapy over an initial six month treatment period ("TAXOL/cisplatin resistant clinical samples").

The data from Tables 11A and 11B was generated from the third study described above, which utilized *ovarian cancer samples*, which led to the identification of genes that are expressed at a relatively high level in the TAXOL/cisplatin resistant clinical samples compared to the TAXOL/cisplatin sensitive clinical samples (Table 11A) and genes that are expressed at a relatively low level in the TAXOL/cisplatin resistant clinical samples compared to the TAXOL/cisplatin sensitive clinical samples (Table 11B). Applicants submit that at page 45, lines 16, 17, 19, and 20 of the specification, Applicants inadvertently stated that the clinical samples were from breast cancer samples. Applicants submit herewith amendments to the specification which accurately reflect that ovarian cancer samples were used in the third study of Example 5.

The Office Action further states:

> [t]he problem with the claims, particularly Claim 3 and narrower Claim 18 is the absence of correlation between the resistance gene chosen and any evidence that the gene has a relationship to TAXOL resistance itself...As provided in Ishikawa, BST-2 is expressed in pancreas, kidney, skeletal muscle, liver, lung, placenta, brain and heart tissues as well as hepatoma, bladder cell carcinoma, glioblastoma, and cervical cell carcinoma cell lines. So absence of a correlation of BST2 or any

> of the genes in the Tables provided renders Claim 18 non-enabled because the gene is not evidenced to be a resistance gene. Its differential expression upon exposure to TAXOL may be indicative of apoptosis, for example, and not TAXOL resistance.

Applicants respectfully traverse the aforementioned rejection. The fact that BST-2 is expressed in the pancreas, kidney and other cell lines, as described in Ishikawa, is not relevant to the present invention, wherein a method for identifying an agent that cannot be used to reduce the growth of breast cancer cells when the expression of BST-2 is *increased* in the presence of TAXOL, is claimed. In contrast, Ishikawa teaches BST-2 expression generally, not an increased expression under specific circumstances. Moreover, Applicants assert that chemotherapeutic agents, such as TAXOL, operate by inducing apoptosis. Thus, if a gene is identified from a sample that when exposed to TAXOL, inhibits apoptosis, by definition it is a TAXOL resistant gene. Accordingly, Applicants respectfully submit that there is a correlation between increased BST-2 expression and TAXOL resistance, as claimed.

The Office Action at page 9 further states:

> [o]ver expression alone is not proof of taxol resistance. Under such a notion, Figure 7 of Ishikawa would illustrate, that heart muscle which appear to express BST-2 at higher levels than the kidney would imply that kidney tissue would be TAXOL sensitive whereas heart tissue would be resistant to TAXOL because BST-2 is over expressed. The specification teaches that for BST-2 three of the four cell lines studied for sensitivity illustrated that expression of BST-2 was present, albeit at lower levels than the two resistant cell lines.

Applicants traverse the foregoing rejection. It is Applicants' position that chemotherapeutic agents have toxicity that is tissue specific and it may well be that kidney tissue is more vulnerable to TAXOL toxicity than is heart muscle. Applicants remind the Examiner that the claims have been amended to refer to breast cancer cells and Applicants have demonstrated that BST-2 is relatively highly expressed in TAXOL resistant breast cancer cell lines as compared to TAXOL sensitive breast cancer cell lines (see Table 9B). This evidence clearly supports the claimed methods.

The Examiner further states that:

> [n]either the specification nor the art teaches how to make and use the invention as broadly as claimed. First, cancer cell lines are not indicative of patient samples...Borbe teaches, 'activity of taxol against malignant glioma cell lines *in vitro* has been shown in several studies. However, despite the remarkable *in vitro* potency of taxol, phase II clinical studies of taxol for primary or recurrent malignant gliomas showed no relevant activity' (page 218, col. 1)...Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment...Furthermore, Orr teaches that the normal cells were used to avoid the genetic complexities associated with established cell lines...In light of the teachings in the prior art, and the general unpredictability concerning the activity of BST-2 in tumor cell lines versus actual tumor tissue, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse the foregoing rejection. The Examiner cites Dermer *et al.*, Orr *et al.*, and Eastham for the proposition that tumor cell lines are a poor representation of patient samples. Applicants submit that tumor cancer cell lines are an appropriate and useful model for studying behavior of tumor cells. Although it is certainly possible to use primary culture of tumor cells, however, primary culture of tumor cells is not routinely used in the art because they can only be passaged a limited number of times and the characteristics of the cells change with each passage. On the other hand, tumor cell lines have consistent behavior from passage to passage. According to Hopfer *et al.*, a copy of which is submitted herewith as Appendix C, primary or early passage cells and cell lines from epithelia "provide useful models for studying cell biology of specific tissues, tumorigenicity, genetic abnormalities, or to help screen for effective methods of gene therapy" Hopfer, U., *et al.*, 1996, *Am. J. Physiol.* 270 (*Cell Physiol.* 39): C1-C11. Hopfer *et al.* provides an account of the "power and usefulness of immortalization methodology, based on the experience of several different laboratories." (Hopfer *et al.*, 1996, pg. C2). Moreover, Geller *et al.*, submitted herewith as Appendix D, provides additional evidence that immortal tumor cells in culture have been "widely applied in studies of oncogenesis, development, and differentiation, as well as serving as model systems for studies of the properties they express" Geller, H., *et al.*, 1991, *J. Cell Biochem* 45: 279-283.

One of skill in the art therefore, routinely relies on the consistent behavior of tumor cell lines across multiple experiments. Moreover, a great deal of important work in understanding tumor behavior has been performed in tumor cell lines. One of skill in the art would thus readily appreciate the acceptance of the use of cell lines in cancer research.

Applicants also submit that the present invention provides sufficient guidance as to how one of skill in the art would use the claimed invention. With respect to the Borbe *et al.* reference, the Examiner notes that "despite the remarkable *in vitro* potency of taxol, phase II clinical studies of taxol for primary or recurrent malignant gliomas showed no relevant activity." Applicants submit that the *in vitro* results were impressive enough for the Federal Drug Administration to approve a phase II human clinical study. As the Examiner is aware, the standard for fulfilling the enablement requirement of 35 U.S.C. §112, first paragraph, is not, for example, evidence of human phase II clinical study, but rather, Applicants must demonstrate that one of ordinary skill in the art could make and use the invention without undue experimentation. Furthermore, Applicants assert that enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted, if routine. See, *In re Wands*, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). Based on the teachings of the specification and the state of the art at the time the application was filed, Applicants submit that one skilled in the art would be able to make and use the claimed methods without undue experimentation.

The Examiner at page 11 asserts that:

> different cancers act in different manners. The specification appears to clearly illustrate that different genes are expressed in relatively higher manners for different cancer cell lines. For example, the specification sample colon, breast, ovarian, and melanoma. The genes which appear to be relatively highly expressed in relatively TAXOL resistant cell lines appear to differ between the different cell lines, indicating that not all genes are differentially expressed in different cancer cell lines. For example, determination that BST-2 is relatively highly expressed in breast cancer cell lines does not provide any indication of how this gene functions in any other type of cancer cell lines. The different variety of cancers affect different genes such that the expression of one gene is not indicative of how the gene would act in a different cancer type.

Applicants respectfully traverse the foregoing rejection. Applicants submit that the present invention teaches methods for determining whether an agent may or may not be used to reduce the growth of cancer cells. However, in the interest of expediting prosecution, and in no way conceding to the validity of the rejection, the instant claims have been amended to be drawn to methods for determining whether TAXOL cannot be used to reduce the growth of breast cancer cells. Applicants however would like to make clear that the application teaches that the methods of the instant invention may be used across different cancers (see, for example, page 11, line 16 through page 12, line 19 of the specification). Applicants assert that the teachings of the present invention constitute a blue print that enables the skilled artisan to practice the methods of the invention across a wide range of cancers without undue experimentation. Applicants teach that the source of the cancer cells used in a particular method will be based on how the method of the present invention is being used. The Applicants' specification discloses that:

> if the method is being used to determine whether a patient's cancer can be treated with an agent, or a combination of agents, then the preferred source of cancer cells will be cancer cells obtained from a cancer biopsy from the patient. Alternatively, a cancer cell line similar to the type of cancer being treated can be assayed. For example if breast cancer is being treated, then a breast cancer cell line can be used. If the method is being used to monitor the effectiveness of a therapeutic protocol, then a tissue sample from the patient being treated is the preferred source. If the method is being used to identify new therapeutic agents or combinations, any cancer cells, *e.g.*, cells of a cancer cell line, can be used (see page 12, lines 11-19 of the specification).

The Office Action, at pages 11-12, states that "determination that BST-2 is relatively highly expressed in breast cancer cell lines does not provide any indication of how this gene functions in any other type of cancer cell lines" to controvert the extension of Example 5 of the instant application to other cancers. However, Applicants submit that there is nothing in the Office Action that conclusively establishes that Applicants' invention would not work in the methods as claimed. Moreover, Applicants respectfully submit that the disclosure of the invention as set forth in the specification must be given the presumption of correctness and operativeness by the PTO, and the only relevant concern of the PTO under the circumstances should concern the truth of the assertions contained in the application. *In re Marzocchi*, 439

F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1967); see also, *In re Bowen*, 492 F.2d 859, 181 U.S.P.Q. 48 (C.C.P.A. 1974). The Office Action however, proffers nothing but a mere conclusion drawn by the Examiner to controvert the truth of Applicants' assertions in the instant application.

Furthermore, Applicants again point out that the instant application provides multiple working examples with regard to the evidence of expression of BST-2 in cancer cells. (See, for example, Example 5). Nevertheless, the Office Action in effect would impose an additional requirement for enablement, a requirement not found in the statute; *i.e.*, a working example for every claimed embodiment. Applicants assert that a working example is not a requirement for enablement (See, *Shanks v. Scheffer*, 204 U.S.P.Q. 781, 783 (Pat. Bd. Inter. 1979). Moreover, "there is no magical relation between the number of representative examples and the breadth of the claims." *In re Borkowski and VanVenroy*, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). Section 112 only requires that the "specification contain a written description of the invention, and the manner and process of making and using it."

Applicants thus submit that the claimed methods prior to the present amendments meet the 35 U.S.C. §112, first paragraph requirements.

The Examiner further asserts that:

> [t]hirdly, the specification appears to only sample TAXOL resistant cell lines, however does not appear subjecting any cancer cells to TAXOL and assaying for BST2 mRNA expression. Since the mechanisms of TAXOL and how the agent works within cells is unknown, merely using cell lines which are 'TAXOL resistant' does not appear to simulate subjecting cells to the TAXOL agent...The specification has not provided any teachings with respect to sampling the expression of mRNA *in vivo*. There is no indication that TAXOL is what causes the different expression patterns of the genes when only TAXOL resistant cells are studied. The specification additionally does not appear to consider that TAXOL affects a gene which is involved in a pathway or cascade which is either upstream or downstream of BST2. Therefore, the apparent relatively high expression of the gene in a TAXOL resistant cell line does not appear to provide correlation to clinical sample which have actually been treated with TAXOL.

Applicants respectfully traverse the aforementioned rejection. In particular, Applicants submit that the Examiner presumes the mechanism of action of TAXOL to be upregulation of a

particular gene. Applicants respectfully submit that "[a]n inventor need not comprehend the scientific principles behind the invention" and that "[t]he inventor's theory or belief as to how the invention works is not a necessary element to satisfy the enablement requirement." *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985). Thus, the disclosure of the precise mechanism of TAXOL and how the agent works within cells is not a prerequisite to the patentability of the present invention. A skilled artisan must be able to practice the methods of the invention by determining whether TAXOL cannot be used to reduce the growth of breast cancer cells. A skilled artisan would be able to do so, based on the teachings in Applicants' specification and the knowledge of one skilled in the art.

Lastly, the Examiner is of the opinion that:

> [f]inally, as clearly admitted and pointed out in the specification, page 41, 'the gene descriptions refer to sequence immobilized on an Affymetrix HUM6000 gene chip and that the names associated with the sequences may not be the actual names of the genes that are hybridizing to the bound probe.' Therefore, the specification appears to indicate[d] that the identification of the actual names of the genes may not be truly what was identified. Therefore, without assaying for the true known gene BST2 it is unpredictable that the sequences hybridizing to the bound probe are in fact the nucleic acid sequences of BST2....Therefore, in order to practice the claimed invention as a whole as broadly as claimed, the skilled artisan would be required to perform extensive additionally experimentation with unpredictable results...to determine how the gene functions in an environment which is different than the cell lines which were studied in the specification...to determine how the gene functions with respect to the specific cancer of interest of the patient...to determine how the application of TAXOL *in vitro* differs, if it does, to the application of TAXOL *in vivo*.

Contrary to the Examiner's assertions, Applicants have identified sequences which have been clearly identified by Applicants (see, for example, Table 9B, which identifies a list of Genes (or EST) and the corresponding GenBank numbers). Applicants submit that the present invention identifies genes that are expressed in cancer cell lines that are either sensitive or resistant to defined chemotherapeutic agents (see, for example, page 5, lines 25-35 of the specification). Applicants also teach the sequence corresponding to the identified genes (see, for example, page 5, lines 31-35 of the specification) and methods for using the sequences of the

present invention to, for example, determine whether an agent, *e.g.*, TAXOL, can be used to reduce the growth rate of breast cancer cells (see, for example, page 5 line 36 through page 6, line 6 of the specification).

With respect to the Examiner's arguments regarding the Affymetrix HUM600 gene chip, the gene annotation was determined after experimentation with the chip. The primers which correspond to each gene are not annotated according to the gene name; rather, the primers are given arbitrary names and the gene annotation is performed subsequently. Therefore, by stating that "the gene descriptions refer to sequence immobilized on an Affymetrix HUM600 gene chip," Applicants are stating that the name corresponds to the primer name which is arbitrary, and by stating that "the names associated with the sequences may not be the actual names of the gene that are hybridizing to the bound probe," Applicants are stating that the name of the location on the chip corresponds to the primer name and not the gene name. The foregoing statements therefore do not mean that Applicants did not know what was being measured, as the Examiner seems to suggest, but rather that gene annotation was performed subsequent to experimentation with the chip.

Furthermore, Applicants submit that "[t]he examiner has the initial burden of establish a reasonable basis to question the enablement provided for the claimed invention." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). It is not necessary for the patent document to read like a production specification. A requirement for some experimentation does not prevent the satisfaction of the enablement requirement (*Northern Telecom, Inc. v. Datapoint Corp.*, 15 U.S.P.Q.2d1321, 1329 (Fed. Cir. 1990)). As established above, a person of ordinary skill in the art would know how to make and/or use the claimed invention. Furthermore, the law has never required an applicant to know the specific method or mechanism by which his invention operates. For example, the Court of Appeals for the Federal Circuit has long held that, "it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 U.S.C. § 112." *Cross v. Iizuka*, 753 F.2d 1040, n.3 (Fed. Cir. 1985). In a more recent case, the Federal Circuit again stated, "[i]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortright*, 163 F.3d

1353, 1359 (Fed. Cir. 1999) (citations omitted) (the court reversed the Board's rejection of certain claims to a treatment for baldness).

Based on the foregoing, Applicants respectfully submit that pending claims fulfill the 35 U.S.C. §112, first paragraph requirements. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Rejection of Claims 3, 6, 12, and 15 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 3, 6, 12, and 15 under 35 U.S.C. §112, second paragraph as being "incomplete for omitting essential steps, such omission amounting to a gap between the steps."

Applicants respectfully traverse the foregoing rejection. In particular, Applicants teach multiple methods for determining whether TAXOL cannot be used to reduce the growth of breast cancer cells. In claims 3, 6, 12, and 15, it is not necessary to recite a step for exposing the breast cancer cells to TAXOL, as one of skill in the art performing the methods would appreciate and be able to identify whether TAXOL could not be used to reduce the growth of breast cancer cells based on the expression level of the genes as determined in step (b) of claim 3. Moreover, Applicants' specification teaches how the expression level may be measured (see, for example, page 13, line 36 through page 15, line 20 of the specification) and how a relative expression level may be determined (see, for example, page 13, lines 8-16 of the specification). Accordingly, Applicants respectfully request that the aforementioned rejection be withdrawn.

Rejection of Claim 15 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 15 under 35 U.S.C. §112, second paragraph, because it is "unclear how the claim further limits claim 3 to which it depends. Claim 3 has been amended to recite TAXOL, rather than an agent. Additionally, the claim lacks antecedent basis for 'said agent.'"

Applicants have cancelled claim 15 rendering this rejection moot.

Rejection of Claims 18, 21, 27, and 30 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 18, 21, 27, and 30 under 35 U.S.C. §112, second paragraph, as being "incomplete for omitting essential steps, such omission amounting to a gap between the steps."

Applicants respectfully traverse the foregoing rejection for the following reasons. Applicants teach that the level of expression refers to the "absolute level of expression of an mRNA encoded by the gene or the absolute level of expression of the protein encoded by the gene (*i.e.*, whether or not expression is or is not occurring in the cancer cells)" (see page 12, lines 27-30 of the specification). Moreover, Applicants also disclose that as an alternative to making determinations based on the absolute expression level of selected genes, "determinations may be based on the normalized expression levels" (see page 12, line 36 through page 13, line 31 of the specification). Furthermore, the present specification teaches how the expression level may be measured, such as measuring the mRNA encoded by the selected genes, (see, for example, page 13, line 36 through page 15, line 20 of the specification); measuring the amount of protein encoded by the selected genes (see page 15, lines 21-29 of the specification); and measuring the activity of the protein encoded by the selected genes (see page 15, line 30 through page 16, line 16 of the specification). Finally, Applicants provide multiple working examples wherein the techniques for determining gene expression were utilized (see, for example, Example 2 at page 40 of the specification).

Applicants further submit that claim 30 has been cancelled, thereby rendering the foregoing rejection moot with respect to that claim.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claim 30 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 30 under 35 U.S.C. §112, second paragraph, because it is "unclear how the claim further limits Claim 18 to which it depends. Claim 18 has been amended to recite TAXOL, rather than an agent. Additionally, the claim lacks antecedent basis for 'said agent.'"

Applicants have cancelled claim 30 and therefore respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 32-33, and 35-36 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 32-33 and 35-36 under 35 U.S.C. §112, second paragraph, because it is "unclear whether the two samples are taken simultaneously such that the samples represent the same time in the treatment process or whether one sample is taken at time point number one and the second sample is taken three weeks later, for example, at time point two and a comparison is made to determine how the expression is changing over time."

Applicants respectfully traverse the aforementioned rejection. The claims clearly state that the samples are obtained "during the course of TAXOL treatment," and thus at any two or more time points, the samples may be obtained. Applicants' specification further teaches when the samples may be obtained. In particular, Applicants disclose that

> it is preferable to obtain a first sample from the patient prior to beginning therapy and one or more samples during treatment. In such a use, a baseline of expression prior to therapy is determined and then changes in the baseline state of expression is monitored during the course of therapy. Alternatively, two or more successive samples obtained during treatment can be used without the need of a pre-treatment baseline sample. In such a use, the first sample obtained from the subject is used as a baseline for determining whether the expression of a particular gene is increasing or decreasing (see page 17, line 35 through page 18, line 5 of the specification).

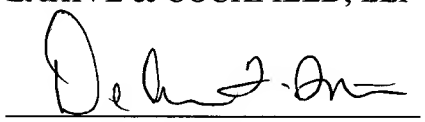
The claims are, therefore, clear and Applicants request that the foregoing rejection be withdrawn.

CONCLUSION

In view of the foregoing, entry into the record of this application of the foregoing amendments and remarks, reconsideration and withdrawal of all the rejections, and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



DeAnn F. Smith, Esq.
Registration No. 36,683
Attorney for Applicants

28 State Street
Boston, MA 02109
(617) 227-7400

Dated: August 13, 2002